pirtobrutinib (Jaypirca™)

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO277

Description

Pirtobrutinib (Jaypirca) is an orally administered non-covalent (i.e., reversable) Bruton Tyrosine Kinase inhibitor (BTKi).

Length of Authorization

- N/A

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
pirtobrutinib (Jaypirca)	Relapsed or refractory mantle cell lymphoma (R/R MCL) after at least two lines of systemic therapy including a BTKi Chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) after at least two prior lines of therapy including a BTK inhibitor and a BCL-2 inhibitor	100mg tablets	60 tablets/30 days
		50 mg tablets	30 tablets/ 30 days

**Quantity limit exceptions not allowed. 50mg dose is only to be used for dose modifications*

Initial Evaluation

I. **Pirtobrutinib (Jaypirca)** is considered investigational when used for all conditions, including but not limited to relapsed or refractory mantle cell lymphoma and chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

II. Pirtobrutinib (Jaypirca) is considered investigational when used for all other conditions, including but not limited to:
   A. Relapsed or refractory mantle cell lymphoma (MCL)
   B. Pirtobrutinib (Jaypirca) used in combination with another oncology therapy
   C. Mantle cell lymphoma (MCL)
   D. Chronic lymphocytic leukemia (CLL)
   E. Small lymphocytic lymphoma (SLL)
   F. Waldenström macroglobulinemia
   G. Marginal zone lymphoma

H. Chronic graft versus host disease

Renewal Evaluation

I. N/A

Supporting Evidence

I. Pirtobrutinib (Jaypirca) is a non-covalent (i.e., reversable) Bruton Tyrosine Kinase inhibitor (BTKi), FDA-approved under an accelerated approval pathway for the treatment of relapsed or refractory mantle cell lymphoma (R/R MCL) after at least two lines of systemic therapy, including a BTKi. Additionally, pirtobrutinib (Jaypirca) was approved under an accelerated approval pathway for the treatment of chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) after at least two prior lines of therapy including a BTK inhibitor and a BCL-2 inhibitor. Continued approval of pirtobrutinib (Jaypirca) is contingent upon verification of clinical benefit in confirmatory trials.
II. Safety and efficacy of pirtobrutinib (Jaypirca) has not been established in a pediatric population.
III. Efficacy and safety of pirtobrutinib (Jaypirca) in combination with other oncology agents has not been evaluated by clinical trials.
IV. The diagnosis and management of MCL and CLL/SLL requires detailed clinical examination in combination with advanced testing. Given the complexities of diagnosis and treatment of these conditions, supervision of treatment by an oncologist or hematologist is required.

Investigational or Not Medically Necessary Uses

I. There are ongoing clinical studies to assess efficacy and safety of pirtobrutinib (Jaypirca) in multiple settings. Pirtobrutinib (Jaypirca) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
    A. Pirtobrutinib (Jaypirca) used in combination with another oncology therapy
    B. Mantle cell lymphoma (MCL)
        i. The efficacy of pirtobrutinib (Jaypirca) in patients with relapsed or refractory MCL was based on an open-label, single-arm, phase 1/2 clinical trial (BRUIN). The trial enrolled patients (N=120) with relapsed or refractory MCL after at least two lines of systemic therapy, including a BTK inhibitor [ibrutinib (Imbruvica), acalabrutinib (Calquence), zanubrutinib (Brukinsa)]. Pirtobrutinib (Jaypirca) was administered as 200mg once a day. The primary efficacy outcome was objective response rate (ORR). Other measured outcomes included complete response (CR), partial response (PR), time to response, and duration of response. Pirtobrutinib (Jaypirca) showed an ORR of 50% (60) of patients. Fifteen (13%) achieved complete

response with the remainder (38%) achieving partial response. Additionally, the time to response was 1.8 months (0.8-4.2) with a median duration of response of 8.3 months (5.7-NE).

ii. The population was treatment experienced with a median of three prior lines of therapy, 93% having received two or more prior lines. All had previously received a BTKi containing regimen; other prior therapies being chemo-immunotherapy (88%), HSCT (20%), lenalidomide (18%), CAR-T therapy (9%).

iii. The safety of pirtobrutinib (Jaypirca) was reported based on the pooled analyses from all cohorts in the phase 1/2 clinical trial. In the pooled safety population, the most common (≥ 20%) adverse reactions included decreased neutrophil count, hemoglobin, platelet count, lymphocyte count, as well as fatigue, musculoskeletal pain, bruising, and diarrhea. Severe adverse reactions specific to the MCL cohort occurred in 38% of patients which included pneumonia (14%), COVID-19 (4.7%), musculoskeletal pain (3.9%), hemorrhage (2.3%), pleural effusion (2.3%), and sepsis (2.3%). Dose reductions were seen in 4.7% of trial participants with therapy interruptions being needed in 32%. Nine percent of patients required permanent discontinuation. Fatal adverse reactions occurred in 7% of patients; most commonly due to infections (4.7%) including COVID-19 (3.1% of all patients). Current patient exposure to pirtobrutinib (Jaypirca) is limited to clinical trial participants; thus, the real-world safety profile and patient experience with this drug remain undefined. Based on a single-arm, open-label clinical trial in a small patient population, the overall safety profile of pirtobrutinib (Jaypirca) is largely unknown.

iv. The quality of the evidence is considered low given the observational nature of the trial with an open-label study design and lack of a comparator arm. Additionally, there remains an unknown clinical impact on the overall survival and health-related quality of life measures. Although overall response rate is an objective measure and may indicate the potential benefit of therapy, it does not predict long term outcomes such as overall survival.

v. As of March 2023, current third and subsequent line therapies for the treatment of R/R MCL are approved based on limited evidence. NCCN guideline directed therapies for third-line and beyond include brexucabtagene autoleucel (TECARTUS), pirtobrutinib (Jaypirca), and allogeneic HCT in eligible patients. Both CAR-T therapy and pirtobrutinib (Jaypirca) are FDA approved for R/R MCL under an accelerated approval pathway. Based on the limited available evidence, there is low confidence to direct to one therapy over another [i.e., brexucabtagene autoleucel (TECARTUS) versus pirtobrutinib (Jaypirca)].

vi. Due to lack of conclusive clinical data to direct a path to curative therapies, NCCN guidelines for MCL note that the best management for any patient with cancer is

in a clinical trial setting, and participation in trial is especially encouraged. Patients participating in clinical trials receive regular care, often at leading health care facilities with experts in the field while participating in important medical research and further advancements in treatment, with close safety monitoring and follow-up. Participation in a clinical trial remains the most favorable treatment option for patients with R/R MCL. Despite the accelerated FDA-approval, continued approval of pirtobrutinib (Jaypirca) as a subsequent-line treatment of MCL, remains contingent upon verification of clinical benefit in confirmatory trials. Additionally, an expanded access program via manufacturer, as part of the ongoing clinical studies of pirtobrutinib (Jaypirca), remains a practical option and an alternative path to treatment for qualifying patients.

C. Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)
   i. The efficacy of pirtobrutinib (Jaypirca) in patients with previously treated CLL/SLL was based on an open-label, single-arm, phase 1/2 arm of a larger clinical trial (BRUIN). The trial enrolled patients (N=108) with CLL/SLL after at least two lines of systemic therapy, including a BTK inhibitor [ibrutinib (Imbruvica), acalabrutinib (Calquence), zanubrutinib (Brukinsa)] and a BCL2 inhibitor. Pirtobrutinib (Jaypirca) was administered as 200mg once a day. The population was treatment experienced with a median of five prior lines of therapy (2-11). All had previously received a BTKi containing regimen [ibrutinib (Imbruvica) (97%), acalabrutinib (Calquence) (9%), zanubrutinib (Brukinsa) (0.9%)] and a BCL-2 inhibitor [venetoclax (Venclexta)].
   ii. The primary efficacy outcome was objective response rate (ORR). Other measured outcomes included complete response (CR), partial response (PR), progression free survival (PFS), time to response, and duration of response. Pirtobrutinib (Jaypirca) had an ORR of 70.0% (95% CI, 60.0 to 78.8) and 79.0% (95% CI, 69.7 to 86.5) when partial response with lymphocytosis was included. No patients in this subgroup were able to achieve a complete response. Additionally, the median time to response was 3.7 months (1.7-27.9) with a median duration of response of 12.2 months (9.3-14.7). Median PFS was 17 months.
   iii. The most common adverse reactions (≥ 20%), excluding laboratory terms, were fatigue, bruising, cough, musculoskeletal pain, COVID-19, diarrhea, pneumonia, abdominal pain, dyspnea, hemorrhage, edema, nausea, pyrexia, and headache. Adverse events of special interest included infections (71%), bleeding (42.6%), and neutropenia (32.5%). The incidence of infection while on pirtobrutinib was higher than with other BTK inhibitors in this cancer type (71% vs 55.6%). Treatment-related adverse events led to dose reductions in 15 patients (4.7%) and permanent discontinuation of pirtobrutinib in nine patients (2.8%).

iv. In total, 18 patients died while receiving pirtobrutinib (Jaypirca). Two died from disease progression. The remaining 16 succumbed to other causes including coronavirus disease 2019 (Covid-19) or Covid-19–related pneumonia (8 patients), pneumonia or fungal pneumonia (2 patients), septic shock or shock (2 patients), and other causes (4 patients).

v. NCCN guidelines recommend use of pirtobrutinib (Jaypirca) for use in certain circumstances should there be resistance or intolerance to prior covalent BTKi therapy. Additionally, it remains as a therapy for relapsed or refractory disease after prior BTKi and venetoclax-based regimens. Use in the both of the settings above carry a category 2A recommendation. The FDA labeled indication specifically states pirtobrutinib (Jaypirca) is for use after therapy with a BTKi and BCL-2 inhibitor. Despite the accelerated FDA-approval, continued approval of pirtobrutinib (Jaypirca) as a subsequent-line treatment of CLL/SLL, remains contingent upon verification of clinical benefit in confirmatory trials.

vi. The quality of the evidence is considered low given the observational nature of the trial with an open-label study design and lack of a comparator arm. Additionally, there remains an unknown clinical impact on the overall survival and health-related quality of life measures. Although overall response rate is an objective measure and may indicate the potential benefit of therapy, it does not predict long term outcomes such as overall survival. Other outcomes measured including PFS may be considered the “gold standard” in this disease state, though other publications consider PFS an “unreliable survival surrogate” as patients with CLL/SLL have increased comorbidities given it is a disease of the mostly elderly who generally succumb to other conditions without disease progression.

D. Waldenström macroglobulinemia
E. Marginal zone lymphoma
F. Chronic graft versus host disease

References

1. Jaypirca. Package Insert. Lilly USA LLC; January 2023.
2. Mato AR, Shah NN, Jurczak W, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. Lancet. 2021;397(10277):892-901. doi:10.1016/S0140-6736(21)00224-5
3. National Comprehensive Cancer Network. B-Cell Lymphoma. NCCN. February 8, 2023. Accessed February 9, 2023. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf
4. Cohen JB, Shah NN, Alencar AJ, et al. MCL-133 Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Previously Treated Mantle Cell Lymphoma: Updated Results From the Phase 1/2 BRUIN Study. Clin Lymphoma Myeloma Leuk. 2022;22 Suppl 2:S394-S395. doi:10.1016/S2152-2650(22)01569-5
5. Lilly. U.S. FDA Approves Jaypirca™ (pirtobrutinib), the First and Only Non-Covalent (Reversible) BTK Inhibitor, for Adult Patients with Relapsed or Refractory Mantle Cell Lymphoma After at Least Two Lines of Systemic Therapy, Including a BTK Inhibitor. Updated January 27, 2023. Accessed January 30, 2023.
6. Pirtobrutinib (Jaypirca) product dossier. Eli Lilly and Company. February 1, 2023.

7. Mato AR, Woyach JA, Brown JR, et al. Pirtobrutinib after a Covalent BTK Inhibitor in Chronic Lymphocytic Leukemia. N Engl J Med. 2023;389(1):33-44. doi:10.1056/NEJMoa2300696
8. National Comprehensive Cancer Network. B-Cell Lymphoma. NCCN. March 11, 2024. Accessed March 24, 2024. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf
9. US Food and Drug Administration. FDA grants accelerated approval to pirtobrutinib for chronic lymphocytic leukemia and small lymphocytic lymphoma. FDA.gov. December 7, 2023. Accessed March 13, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pirtobrutinib-chronic-lymphocytic-leukemia-and-small-lymphocytic

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
acalabrutinib (Calquence®) Policy	Mantle cell lymphoma (previously treated)
	Chronic lymphocytic leukemia (CLL)
	Small lymphocytic lymphoma (SLL)
ibrutinib (IMBRUVICA®) Policy	Mantle cell lymphoma (previously treated)
	Marginal zone lymphoma (relapsed/refractory)
	Chronic graft-versus-host disease (refractory)
	Chronic lymphocytic leukemia/Small lymphocytic lymphoma
	Waldenström macroglobulinemia
zanubrutinib (Brukinsa™) Policy	Mantle cell lymphoma
	Waldenström macroglobulinemia
	Chronic lymphocytic leukemia/Small lymphocytic lymphoma
	Relapsed or refractory marginal zone lymphoma in adults who have received at least one anti-CD20-based regimen
venetoclax (Venclexta®) Policy	Chronic lymphocytic leukemia/Small lymphocytic lymphoma
	Acute myeloid leukemia
duvelisib (Copiktra®) Policy	Relapsed/refractory chronic lymphocytic leukemia (CLL)
	Relapsed/refractory small lymphocytic lymphoma (SLL)
idelalisib (Zydelig®) Policy	Relapsed Chronic Lymphocytic Leukemia (CLL)
lenalidomide (Revlimid®), pomalidomide (Pomalyst®), thalidomide (Thalomid®) Policy	Follicular lymphoma
	Mantle cell lymphoma
	Marginal zone lymphoma
	Multiple myeloma
	Multiple myeloma maintenance therapy following auto-HSCT
	Myelodysplastic syndromes

Policy Implementation/Update:

Action and Summary of Changes	Date
Added SLL/CLL indication to E/I section with supporting evidence. Moved R/R MCL supporting evidence to E/I section. Updated related policies table.	4/2024
Policy created	05/2023